

REMARKS

Claims 1-11 are pending in this application. By this Amendment, claims 1, 3, 5, 6, 9 and 11 are amended. No new matter is added.

Objections to Specification

The Office Action objects to the specification for containing an asserted informality. Applicants believe that this objection is overcome with the above amendment to the specification in which the paragraph on lines 11-12 of the specification is amended to read "Several compounds analogous to Distamycin A and derivatives thereof are known in the art." Reconsideration and withdrawal of the objection to the specification are respectfully requested.

§ 101 Rejection

The Office Action rejects claim 11 under 35 U.S.C. § 101 because the claimed invention is asserted to be directed to non-statutory subject matter. In particular, the Office Action asserts that a use is not a statutory class of invention. Applicants believe that this rejection is overcome with the above amendment to claim 11. Reconsideration and withdrawal of the rejection of claim 11 under 35 U.S.C. § 101 are respectfully requested.

§ 112, Second Paragraph, Rejection

The Office Action rejects claims 1-4 and 6-11 under 35 U.S.C. § 112, second paragraph, as being indefinite for containing asserted informalities.

Regarding claim 1, Applicants have amended the claim to further clarify that “a) if an R₄, R₅, or R₆ group is present, then at least 1 of R₄, R₅ and R₆ is alkyl;”

Regarding claim 9, Applicants have changed “the human” to --a human-- as suggested by the Examiner.

Regarding claim 11, Applicants believe this aspect of the rejection is overcome with the above-discussed amended claim 11.

For at least these reasons, reconsideration and withdrawal of the rejection of claims 1-4 and 6-11 under 35 U.S.C. § 112, second paragraph, are respectfully requested.

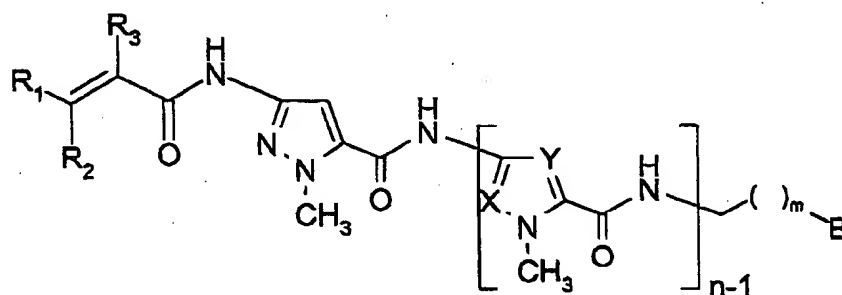
Rejections to Claims

The Office Action objects to claims 1-11 for containing additional asserted informalities. Applicants have corrected the typographical errors noted in claims 1, 3, 5 and 6 by the Examiner. Reconsideration and withdrawal of the objection to claims 1-11 are respectfully requested.

§ 103 Rejections

The Office Action rejects claims 1-11 under 35 U.S.C. § 103(a) as being obvious over WO Patent Application 98/04524 in view of WO Patent Application 96/05196. Claims 1-11 are additionally rejected under 35 U.S.C. § 103(a) as being obvious over the same two WO patent applications and further in view of Baraldi et al. ("Synthesis and Antitumor Activity of Novel Distamycin Derivatives"). These rejections are traversed as they may apply to the amended claims.

Applicants have amended the general formula so as to cover derivatives of formula (I) wherein the acryloylanino moiety is first connected with a pyrazole ring [X=N and Y=CH in the first ring on the left], as follows:



wherein any of the parameters is as defined in the specification.

As reported in the instant specification, several distamycin derivatives are known in the art, each comprising structural modifications to distamycin A itself. Baraldi discloses distamycin derivatives bearing an acryloyl moiety and a poly-heterocyclic central chain not solely consisting of pyrrole units. See, in particular, derivatives 12 and 13 on page 1242 of the same. Likewise, WO 96/05196 refers to a variety of compounds also possessing a central core not exclusively formed by pyrrole units.

Both prior art references, therefore, teach to prepare distamycin derivatives wherein the poly-pyrrole chain of distamycin A does not appear as an essential requirement for retaining biological activity.

On the opposite side, WO 98/04524 does not seem to represent a relevant piece of prior art as it only discloses distamycin derivatives with a central polypyrrole chain. As it does not teach nor suggest to modify the polypyrrole skeleton of distamycin, Applicants respectfully submit that WO 98 should be thus disregarded.

In addition to the above, it is worth noting that even if WO 96/05196 discloses a broad class of derivatives, it provides biological data for a lead compound not possessing the acryloyl moiety (see page 32, lines 3-7 of the same). From the above it can be concluded that even if the central polypyrrole portion of distamycin A were to have somehow been replaced by other heterocycles, just as per WO 96, better results can be anyway obtained if these same molecules also possess the so-called mustard group (not the acryloyl group), that is to say that the terminal portion of the molecule represented by a N,N-bis(2-chloroethyl)amino-benzene group.

The most relevant art cited is thus represented by Baraldi which teaches to prepare distamycin derivatives possessing 3 pyrrole units and one additional heterocycle such as pyrazole or imidazole (see scheme 1, page 1242), the former retaining higher activity (compare IC50 values for compounds 13 with 12, table I, page 1244).

Applicants respectfully submit that even by using the teaching of Baraldi, that is by preparing distamycins having an acryloyl moiety linked to a first pyrazole ring and subsequently connected with 3 pyrrole units, Applicants prepared novel compounds

consistently possessing a superior activity, expressed in terms of IC50. Unexpectedly, said additional improvement appears to be related to the modification of the terminal amidino group being replaced by additional nitrogen containing ending B groups, as per the presently claimed invention.

Whilst compound 13 of Baraldi is endowed with a inhibitory activity (IC50) equal to 9.9, two additional compounds of the invention corresponding to the above derivative 13 but having a N-methyl-amidino group or a cyano-amidino group, were endowed with a superior inhibitory activity (see the enclosed table).

To sum up, whilst the prior art as a whole teaches to modify the central polyheterocyclic core of distamycin and the "left" portion of the molecule being a mustard or an acryloylamino group, the presently claimed invention unexpectedly provides novel compounds which, whilst possessing a remarkable IC50 inhibitory activity, have different terminal B groups (on the right side of the molecule).

No indications arises from the prior art to modify the B group and also the polyheterocyclic chain with the expectation of getting particularly active compounds.

For at least the above reasons, reconsideration and withdrawal of the rejections of claims 1-11 under 35 U.S.C. § 103(a) are respectfully requested.

Conclusion

Applicants respectfully submit that this application is in condition for allowance and such action is earnestly solicited. If the Examiner believes that anything further is desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact Applicants' undersigned representative at the telephone

number listed below to schedule a personal or telephone interview to discuss any remaining issues.

Please charge any fee deficiency or credit any overpayment to Deposit Account No. 01-2300.

Respectfully submitted,

A handwritten signature in black ink, reading "Robert K. Carpenter". The signature is written in a cursive style with a horizontal line underneath.

Robert K. Carpenter
Registration No. 34,794

ARENT FOX KINTNER PLOTKIN & KAHN, PLLC
1050 Connecticut Avenue, N.W.,
Suite 600
Washington, D.C. 20036-5339
Tel: (202) 857-6000
Fax: (202) 638-4810

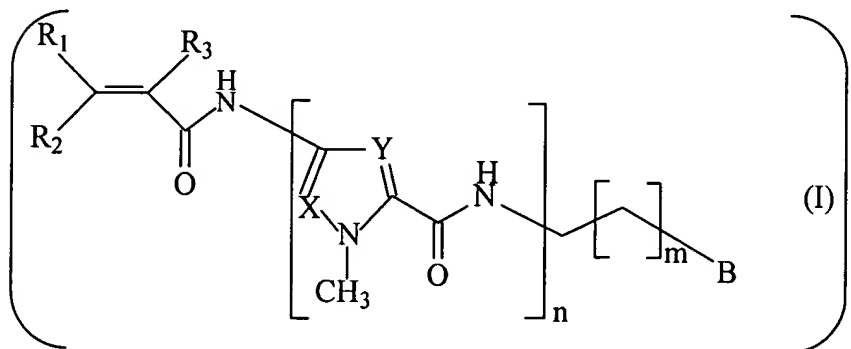
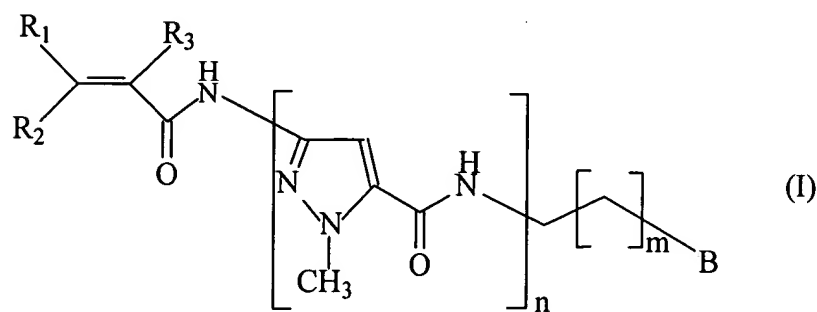
Attachments: Marked-Up Amendments to the Specification and Claims
Comparison Data

MARKED-UP AMENDMENTS TO THE SPECIFICATION AND CLAIMS

The paragraph on page 1, lines 11-12 of the specification is amended as follows:

--Several compounds analogous is Distamycin A and derivatives thereof are known in the art.--

1. (Amended) A compound which is an acryloyl substituted distamycin derivative of formula



wherein:

n is 2, 3 or 4;

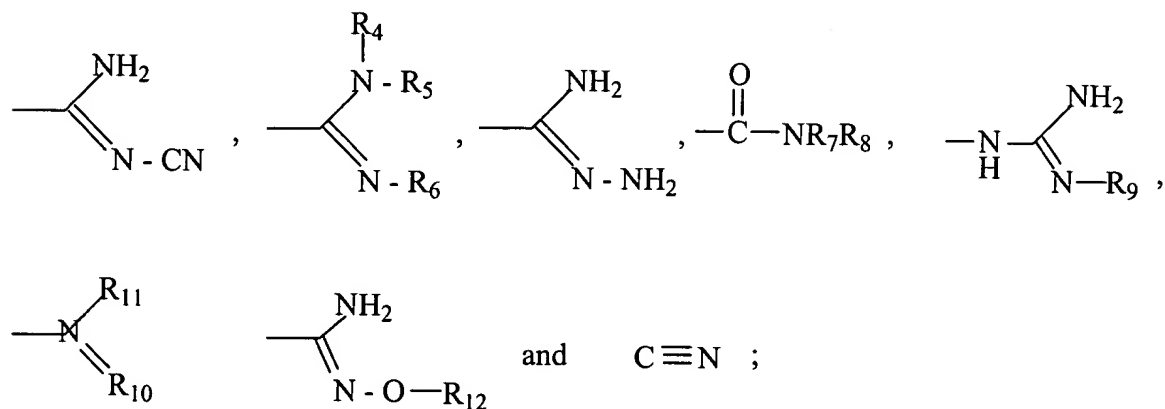
m is 1 or 2;

[X and Y are the same or different and are selected, independently for each heterocyclic ring of the [polyetherocyclic] chain, from N and CH;]

R₁ and R₂, which are the same or different, are selected from hydrogen, halogen, and C₁-C₄ alkyl;

R₃ is hydrogen or halogen;

B is selected from



wherein R₄, R₅, R₆, R₇, R₈, R₁₀, R₁₁ and R₁₂ are, independently from each other,

hydrogen or C₁-C₄ alkyl; and R₉ is hydrogen or hydroxy;

or a pharmaceutically acceptable salt thereof;

provided that

- a) if an R₄, R₅ or R₆ group is present, then at least one of R₄, R₅ and R₆ is alkyl; and
- b) at least one of the heterocyclic rings within the polyheterocyclic chain is other than pyrrole[; and
- c) X and Y are not both N for the same heterocyclic ring].

3. (Twice Amended) A compound according to claim 1' wherein

[X and Y are as defined in claim 1;]

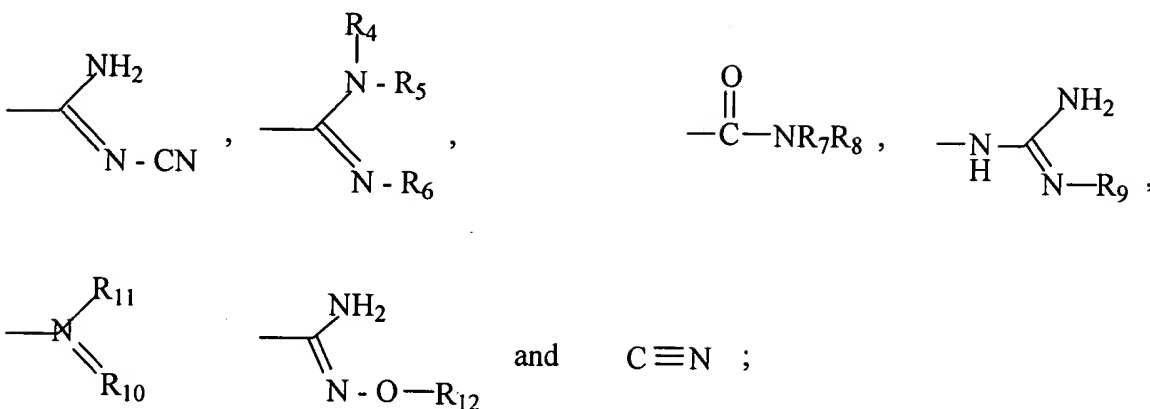
n is 3 or 4;

m is 1;

R₁ and R₂ are hydrogen;

R₃ is chlorine or bromine;

B is selected from



wherein R₄, R₅, R₆, R₇, R₈, R₁₀, R₁₁ and R₁₂ are, independently from each other, hydrogen or methyl; and R₉ is hydrogen.

5. (Amended) A compound selected from the group consisting of:
3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α-bromoacrylamido)-pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propioncyanamidine;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamide;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamide;

- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propyl-N,N-dimethylamine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-O-methylamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-O-methylamidoxime;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propioncyanamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido)) pyrrole-2-carboxamido propionamide;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamide;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -chloroacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propyl-N,N-dimethylamine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -chloroacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-O-methylamidoxime;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -chloroacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-O-methylamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamide;

- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propioncyanamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamide;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N-dimethylamine;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-O-methylamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;
- 3 - (1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrazole-5-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrazole-5-carboxamido) propion-N,N'-dimethylamidine;
- 2 - (1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrazole-5-carboxamido) ethylguanidine;
- 3 - (1-methyl-3-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrazole-5-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) imidazole-2-carboxamido) propion-N-methylamidine;

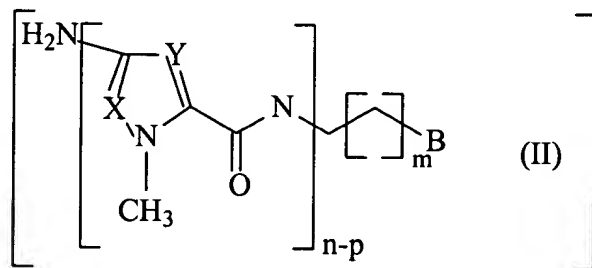
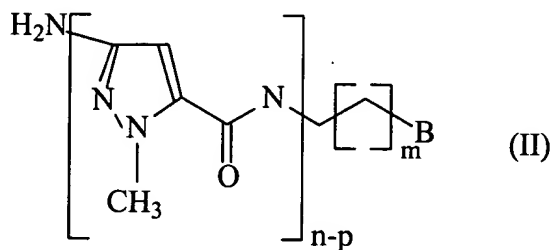
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) imidazole-2-carboxamido) propionamide;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) imidazole-2-carboxamido) ethylguanidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) imidazole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) imidazole-2-carboxamido)-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propioncyanamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamide;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -chloroacrylamido)pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-3-(α -bromoacrylamido) pyrazole-5-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) [propioncyanamidine] propioncyanamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N'-dimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N,N'-trimethylamidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamide;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N-methylamide;
- 2 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) ethylguanidine;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-N,N-dimethylamine;

- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propion-0-methylamidoxime;
- 3 - (1-methyl-4-(1-methyl-4-(1-methyl-4-(α -bromoacrylamido) imidazole-2-carboxamido) pyrrole-2-carboxamido) pyrrole-2-carboxamido) propionitrile; and the pharmaceutically acceptable salts thereof.

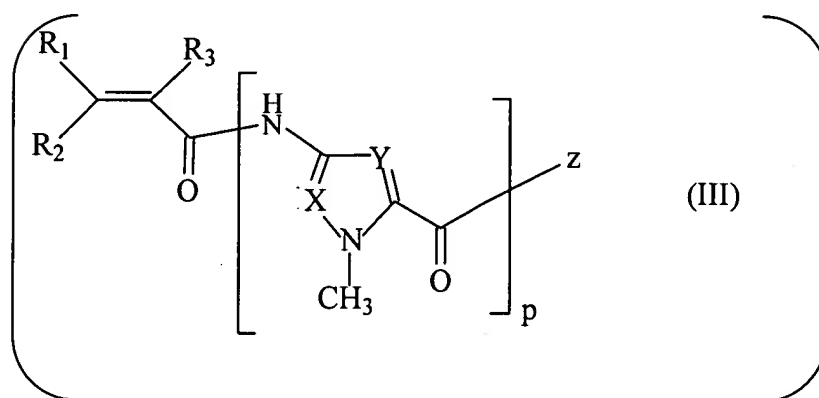
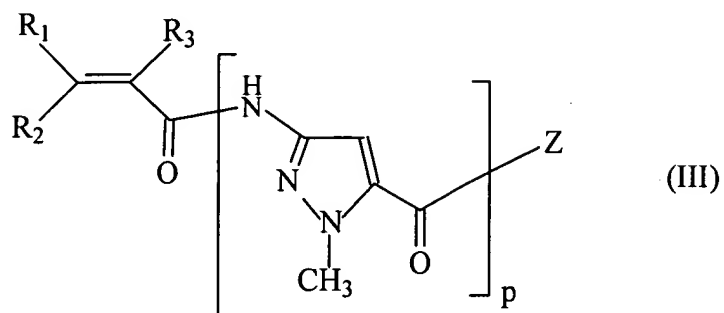
6. (Amended) A process for preparing a compound as defined in claim 1, which process comprises:
- (a) reacting a compound of formula:



wherein n, m, [X, Y] and B are as defined in claim 1;

p is 0 or 1;

with a compound of formula:



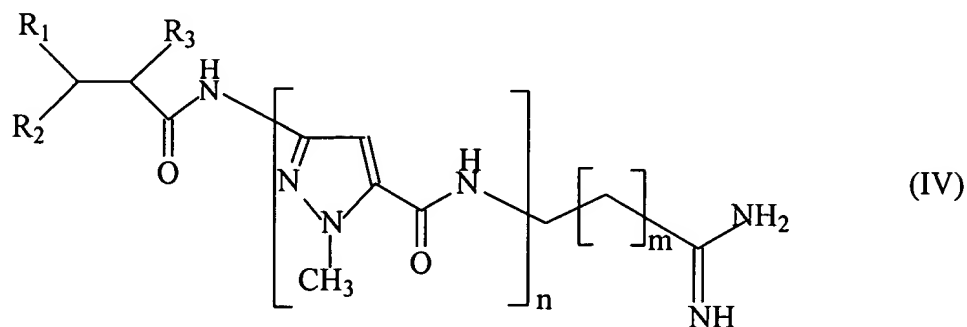
wherein R_1 , R_2 , and R_3 , [X and Y] are as defined in claim 1;

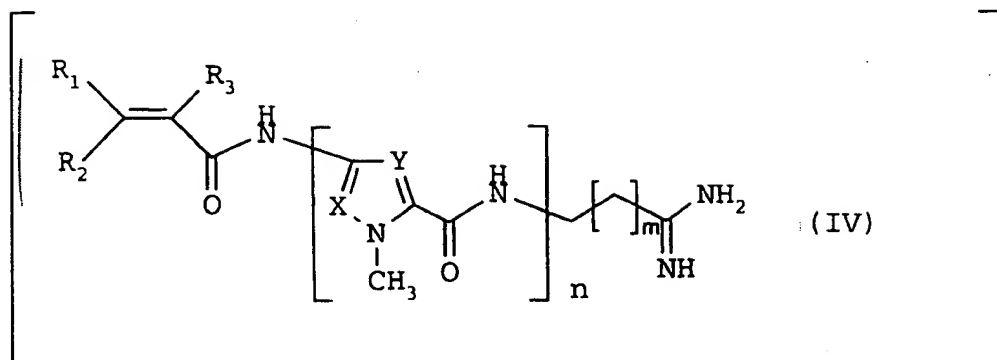
p is as defined above;

z is hydroxy or a leaving group;

or:

(b) when B is equal to $-C\equiv N$, reacting a compound of formula:





wherein n , m , R_1 , R_2 , and R_3 , [X and Y] are as defined above;

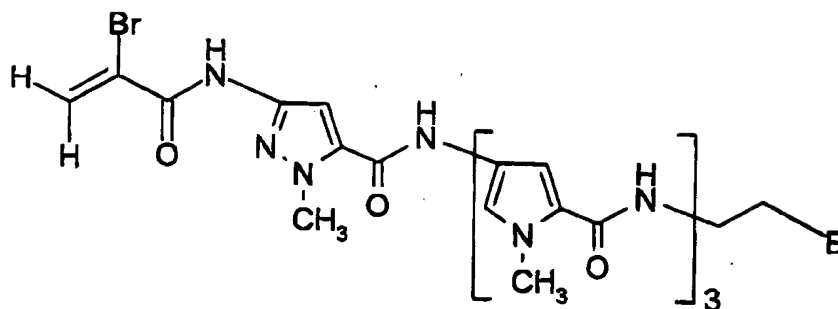
with succinic anhydride; and,

(c) if desired, converting a compound of formula (I) into a pharmaceutically acceptable salt thereof.

9. (Amended) A compound as defined in claim 1 for use in a method of treatment of [the] a human or animal body by therapy.

11. (Amended) A method of manufacturing a medicament for use as an antitumor agent comprising [Use of] utilizing a compound as defined in claim 1 [in the manufacture of a medicament for use as an antitumor agent].

Enclosure



Compound	B	IC50 (ng/ml)
13 of Baraldi		9.9
Compound A		7.8
Compound B		5.6

Compounds A and B of the invention are reported in Example 1 (page 21 of WO 99/50265) and Example 2 (page 24,25 of the same), respectively.